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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/590,724	08/25/2006	Lars Burgdorf	MERCK-3229	2551

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EXAMINER	
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ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/590,724	BURGDORF ET AL.	
	Examiner	Art Unit	
	Paul Zarek	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/04/2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *11-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08/25/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 3-8, 12-18, 23, and 26-32 have been amended by the Applicant in correspondence filed on 08/25/2008. Claims 1-32 are currently pending. This is the first Office Action on the merits of the claim(s).

Election/Restrictions

2. Applicant's election with traverse of Group I, drawn to a compoound of formula I wherein Ar^1 and Ar^2 are phenyls, Ar^3 is pyridyl, and Z is -O-, and the elected species of N-methyl-4-[3-(2-methoxy-5-trifluoromethylphenylcarbamoyl)phenoxy]pyridine-2-carboxamide (tosylate) (compound 16)in the reply filed on 12/04/2008 is acknowledged. The traversal is on the ground(s) that the Examiner has not established that it would be an undue search burden to examine the claims, *in toto*. This is not found persuasive because the requirement for restriction in a 371 application is not based on the presence of an undue search burden; rather, it is based on unity of invention as indicated by the presence of a special technical feature. The Requirement for Restriction/Election of Species mailed on 11/05/2008 clearly demonstrated that the prior art teaches an embodiment of Claim 1, therefore removing any special technical feature linking the claims.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 1-10 read on the elected species. Claims 11-32 are withdrawn as being drawn to a nonelected group.

Priority

4. Applicant's claim for the benefit of a prior-filed international EP05/00273 (filed on 01/13/2005) application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows: Applicant has not properly claimed the benefit of the prior-filed international application. To gain the benefit of a prior filed application, "[t]he later-filed application must contain a reference to the prior-filed application in the first sentence(s) of the specification or in an application data sheet, for a benefit claim under 35 U.S.C. 120, 121, or 365(c), and also for a benefit claim under 35 U.S.C. 119(e)." (MPEP 201.11(C)). The effective filing date of the instant application is 08/25/2006.

5. Acknowledgment is made of applicant's claim for foreign priority to German application 10 2004 009 238.9 (filed on 02/26/2004) under 35 U.S.C. 119(a)-(d). The German application was filed more than a year prior to the filing of the instant application, and, hence, Applicant cannot claim priority to said document. There is currently no foreign priority of the instant application. Applicant may gain the foreign priority by perfecting the claim for the benefit of the prior-filed international application EP05/00273.

Information Disclosure Statement

6. The information disclosure statement filed 08/25/2006 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that

portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Claim Rejections - 35 USC § 112 (1st paragraph)

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for pharmaceutically acceptable salts and stereoisomers of compounds of formula I limited to the elected group, does not reasonably provide enablement for solvates and derivatives of compounds of formula I. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

9. *In re Wands*, 858 F.2d at 736-40, 8 USPQ2d at 1403-07, set forth eight factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." (MPEP § 2164.01(a))

a. *The breadth of the claim*: The rejected claims are drawn to a compound of formula I, and pharmaceutically acceptable salts, derivatives, solvates and stereoisomers, thereof. The instant specification defines solvates to include hydrates and alcoholates. Derivatives are defined as salts and prodrugs;

b. *Nature of the invention*: The nature of the invention is compounds of formula I, salts and stereoisomers thereof;

c. *The state of the prior art*: Prodrugs are known in the art and are utilized to improve the targeting or pharmacokinetics of a given drug. Van de Waterbeemd, et al. (Journal of Medicinal Chemistry, 2001), teach the myriad considerations one must keep in mind when designing prodrugs (pgs 1314-1327).

Approximately one third of drugs are capable of forming crystalline hydrates (Vippagunta, et al., Advanced Drug Delivery Reviews, 2001, pg 15, section 3.1).

Byrn, et al. (Solid State Chemistry of Drugs, 1999), teach that "[t]he occurrence of hydrated or solvated crystal forms, crystals in which solvent molecules occupy regular positions in the crystal structure, is widespread but by no means universal among drug substances." (pg 232, emphasis added). Most drug crystals that fall into the category of solvates are hydrates (pg 236).

Byrn, et al., note that the water molecule is particularly suited to fill structural voids, due to its small size. In hydrated crystal structures, water molecules bind to other water molecules but also to any available functional group, i.e. carbonyls, amines, alcohols, and many others which are capable of accepting or donating an active hydrogen atom to form hydrogen bonds (pg 236, "Hydrates"). The behavior of hydrates of pharmaceuticals is unpredictable due to dehydration prior to melting, and cracking during dehydration (pg 234). Also hydrates and solvates may only be formed under certain conditions, dependent upon the compounds sought to be crystallized. Such a process is

not a given in pharmacology and requires a great deal of research, with no reasonable expectation of success.

Furthermore, the stability of solvates and hydrates is not altogether predictable, wherein said stability directly affects the properties of a given molecule. This lack of stability means that a hydrate or solvate, if found to possess similar properties as the target compound, may not function as intended, *in vivo*. Such facts lead to the conclusion that more than a mere recitation is needed in order to support a claim to solvates and hydrates. Creating functional solvates and hydrates with the same properties as the mother-compound is by no means routine, thus there must be a showing sufficient to satisfy the enablement requirement;

d. *Level of one of ordinary skill in the art*: Medicinal chemists would represent one of ordinary skill in the art. Consequently, the level of ordinary skill would be high;

e. *Level of predictability in the art*: Numerous factors must be considered when attempting to create a prodrug. Van de Waterbeemd, et al., state that even with high-throughput screening and combinatorial chemistry, "the attrition of the eventual development candidates is still very high mainly due to toxicity and/or poor [pharmacokinetic] properties" (pg 1327, "Future Directions" paragraph 1, emphasis added). It cannot be known *a priori* whether a given molecule will be an effective prodrug. High-throughput computer modeling is not yet competent to reliably predict whether a given molecule would be an effective prodrug of a given drug. As such, "there remains a need for relatively low-throughput animal studies to extrapolate the likely clinical pharmacokinetic profile (van de Waterbeemd, et al., pg 1328, paragraph 1). Van

de Waterbeemd, et al., further teach that it is unclear which mathematical models would be most suited to predict pharmacokinetic properties of a given molecule in lieu of experimental data (pg 1328, paragraph 3). Finally, van de Waterbeemd, et al., discuss that "much needs to be learned about transporters influencing either active drug uptake or efflux of orally administered drugs. In addition, it will be important to develop screens to assess its extent" (pg 1328, "Conclusions).

Just because many drugs are capable of forming hydrates or solvates does not mean that the resulting hydrate or solvate can be predicted before hand. Vippagunta, et al., teach that predicting the formation of solvates or hydrates of a compound is "complex and difficult." "There may be too many possibilities so that no computer programs are currently available for predicting the crystal structures of hydrates and solvates." pg 18, Section 3.4). Byrn, et al., disclose that the properties of solvates and hydrates of a given drug can only be determined empirically;

f. *Amount of direction provided by the inventor*: Applicant defines derivatives to include salts and pro-drugs, and alleges that derivatives "are known in [sic] the person skilled in the art." (pg 22, lines 18-21) Applicant cites art to indicate as such. Applicant defines solvates to mean adductions of inert solvent molecules onto the compounds of formula I (pg 23, lines 5-6);

g. *Existence of working examples*: Applicant discloses 29 compounds. There are no working examples of a prodrug or metabolite or solvate of a compound of formula I; and,

h. *Quantity or experimentation needed to make or use the invention based on the content of the disclosure*: Predicting if a certain molecule is in fact a prodrug that

produces the active compound metabolically, *in vivo*, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo*, this is still an experimental science. For a compound to be a prodrug, it must meet three tests: A) it must itself be biologically inactive; B) it must be metabolized to a second substance, *in vivo*, at a rate and to an extent to produce that second substance at a physiologically meaningful concentration; and C) the second substance must be clinically effective. Determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation. The instant specification does not provide enabling guidance sufficient that one of ordinary skill in the art would understand which of the potentially limitless candidates would be a legitimate prodrug of the compound of formula I. The prior art does not compensate for this deficiency.

Byrn, et al., and Vippagunta, et al., are explicit in their statements that the formation of solvates or hydrates can not be known without experimentation. Indeed, one of ordinary skill in the art could not ascertain which solvates or hydrates would form with any reasonable expectation of success. The instant specification does not make up for this deficiency, as there is no guidance to an ordinarily skilled artisan to either make a solvate or hydrate of a compound of formula I. Undue and unpredictable experimentation would be required to use the invention as claimed. Therefore, the instant specification and prior art would not enable one of ordinary skill in the art at the time the invention was made to make and use the invention commensurate with the scope of the rejected claims.

10. Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds of formula I in which Ar^1 is phenyl mono- or disubstituted by R^1, Ar^2 is unsubstituted phenyl, Ar^3 is pyridinyl monosubstituted by R^1, Y is O or S, Z is CR^1R^1, R^2 is H, and R^1 may be selected from the group consisting of -H, A (as defined by Claim 1), halogen, -OH, -OA, $-CF_3$, and -CONHA, does not reasonably provide enablement for compounds of formula I in which the substituents are other than those listed above. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The Wands factors are discussed below:

a. *The breadth of the claim*: see above;

b. *Nature of the invention*: see above;

c. *The state of the prior art*: Compounds similar in structure to those of formula I are known kinase inhibitors. Dumas, et al. (International Application No. 02/062763), teach similar compounds as raf kinase inhibitors (i.e. compound C2a, pg 51). Brown and Brown (International Application No. WO 99/59959) teach similar compounds as p38 kinase inhibitors (abstract and pg 2 lines 24-27);

d. *Level of one of ordinary skill in the art*: see above;

e. *Level of predictability in the art*: The pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher* (427 F. 2d 833, 166USPQ 18 (CCPA 1970)) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. The

level of unpredictability in this art is very high. As demonstrated by Dumas, et al., and Brown and Brown, similar compounds inhibit distinct, unrelated enzymes;

f. *Amount of direction provided by the inventor*: Applicant disclose that the claimed compounds are inhibitors of raf kinase;

g. *Existence of working examples*: All of the disclosed embodiments fall within particularly preferred embodiments (pg 19, lines 23-31), to which this scope of enablement applies. Applicant has tested only the 29 disclosed compounds and states that these compounds inhibit VEGF-stimulated mitogenesis of human umbilical vascular endothelial cells TIE-2 kinase phosphorylation (Example 3, Methods 3 and 5). It is noted that Applicant did not show the results of these experiments; and,

h. *Quantity or experimentation needed to make or use the invention based on the content of the disclosure*: Applicant has made and tested only a very small subset of the possible compounds encompassed by the rejected claims. The instant specification does not provide sufficient guidance to enable one of ordinary skill in the art at the time the invention was made to make all of the huge number of compounds claimed. "Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. . . . [M]ost syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence" (Dorwald, Side Reactions in Organic Synthesis, 2005).

Moreover, Applicant has not provided any data suggesting that any molecule other than the small, disclosed subset of compounds would be effective raf kinase inhibitors. The possible embodiments claimed are not necessarily obvious variants of each other. "A patent is not a hunting license. It is not a reward for search but compensation for its successful conclusion and patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable." (*Genentech Inc v Nova Nordisk* 42 USPQ 2d 1001) One of ordinary skill could not reasonably determine whether the claimed compounds would be effective raf kinase inhibitors. Indeed, Brown and Brown demonstrate that related compounds inhibit a different kinase (p38) The instant specification does not enable one of ordinary skill in the art to make and use the invention commensurate with the scope of the rejected claims. Undue and unpredictable experimentation would be required.

Conclusions

8. Claims 1-10 are rejected.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul Zarek whose telephone number is (571) 270-5754. The examiner can normally be reached on Monday-Thursday, 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

PEZ

/Rita J. Desai/
Primary Examiner, Art Unit 1625